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SEARCH REQUEST FORM

Requester's Full Name: 10/26/11 (Katy) J. Nida Examiner #: 1134 Date: 11/21/11
 Art Unit: 1626 Phone Number: 2-0707 Serial Number: 10628, 1049
 Location (Bldg/Room#): KEY (Mailbox #): 540 Results Format Preferred (circle): PAPER DISK

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: Hex phosphide inhibitor of neu-
Inventors (please provide full names): Besterina, et al

Earliest Priority Date: _____

Search Topic:

Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Z search pd Z (see claims 5) X is C, (i.e. alkylene,
 cycloalkylene, heteroalkylene,
 heteroaryl.
 Y is O, or C.

II Sec. 4 of Ch. 22

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Searcher Phone #: 22504

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Date Searcher Picked Up: 12/8/01

Date Completed: _____

Searcher Prep & Review Time: 11

Online Time: _____ 798

Type of Search

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Other

Vendors and cost where applicable

✓ STN Dialog

_____ Questel/Orbit _____ Lexis/Nexis

_____ Westlaw _____ WWW/Internet

In-house sequence systems

Commercial Oligomer Score/Length

Interference SPDI Encode/Transl

Other (specify) _____



STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 172095

TO: Rei-Tsang Shiao
Location: 5a10 / 5c18
Thursday, December 08, 2005
Art Unit: 1626
Phone: 571-272-0707
Serial Number: 10 / 628649

From: Jan Delaval
Location: Biotech-Chem Library
Remsen 1a51
Phone: 571-272-2504

jan.delaval@uspto.gov

Search Notes



STIC SEARCH RESULTS FEEDBACK FORM

Biotech-Chem Library

Questions about the scope or the results of the search? Contact **the searcher or contact:**

Mary Hale, Information Branch Supervisor
22507, Remsen 1d86

Voluntary Results Feedback Form

➤ I am an examiner in Workgroup: Example: 1610

➤ Relevant prior art **found**, search results used as follows:

- ☐ 102 rejection
- ☐ 103 rejection
- ☐ Cited as being of interest.
- ☐ Helped examiner better understand the invention.
- ☐ Helped examiner better understand the state of the art in their technology.

Types of relevant prior art found:

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature
(journal articles, conference proceedings, new product announcements etc.)

➤ Relevant prior art **not found**:

- ☐ Results verified the lack of relevant prior art (helped determine patentability).
- ☐ Results were not useful in determining patentability or understanding the invention.

Comments:

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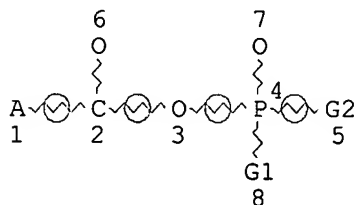
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L13 STR



VAR G1=O/X

VAR G2=C/O

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 8

STEREO ATTRIBUTES: NONE

L15 197 SEA FILE=REGISTRY SSS FUL L13

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197 ANSWERS

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FILE 'HCAPLUS' ENTERED AT 07:38:45 ON 08 DEC 2005

L1 2 S (US20050119233 OR US20020022607 OR US6599889 OR US6608046)/PN
L2 2 S (US2003-628649# OR US2001-797308# OR US2000-582255# OR WO98-U
L3 2 S L1,L2
E BESTERMAN J/AU
L4 75 S E3-E8,E11
E RAHIL J/AU
L5 24 S E3-E6
E PRATT R/AU
L6 520 S E3-E28
E PRATT REX/AU
L7 11 S E3,E4
E METHYLGENE/PA,CS
L8 38 S E3-E10
E METHYL GENE/PA,CS
SEL RN L3

FILE 'REGISTRY' ENTERED AT 07:42:47 ON 08 DEC 2005

L9 67 S E1-E67
L10 1 S 9073-60-3
L11 60 S L9 AND P/ELS
L12 6 S L11 AND (OPOC3 OR OPOC3-C6)/ES
L13 STR
L14 10 S L13
L15 197 S L13 FUL
SAV TEMP L15 SHIAO628/A
L16 64 S L15 AND (OPOC3 OR OPOC3-C6)/ES
L17 64 S L12,L16
L18 133 S L15 NOT L17
L19 25 S L18 AND (C3H5O4P OR C8H4O8P2 OR C3H3O5P OR C10H9O4P OR C8H7O4
L20 24 S L19 NOT C6-C6/ES
L21 16 S L17 AND (C7H4BRO4P OR C9H6O5P OR C5H7O6P OR C9H9O5P OR C7H4O5
L22 14 S L21 NOT (13237-77-9 OR 13237-77-9/CRN)
L23 50 S L17 NOT L22
L24 38 S L20,L22,L12
SAV TEMP L24 SHIAO628A/A

FILE 'HCAOLD' ENTERED AT 08:09:22 ON 08 DEC 2005

L25 10 S L24
SEL AN
EDIT E68-E77 /AN /OREF

FILE 'HCAPLUS' ENTERED AT 08:09:57 ON 08 DEC 2005

L26 19 S E68-E77
SEL AN 2 4 5 7 9 11 13 19
L27 11 S L26 NOT E78-E93
L28 39 S L24
L29 6 S L3-L8 AND L27,L28

L30 10678 S L10
L31 13255 S BETA LACTAMASE
L32 3644 S PENICILLINASE
L33 6 S L27,L28 AND L30-L32
L34 6 S L29,L33
L35 29 S L28 AND (PY<=1997 OR PRY<=1997 OR AY<=1997)
L36 7 S L27 AND L35
L37 11 S L27,L36
L38 20 S L35 NOT L34,L37
L39 0 S L38 AND (PHARMACEUT? OR PHARMACOL?)/SC,SX
L40 1 S L38 AND (1 OR 63)/SC,SX
L41 7 S L24(L) (THU OR BAC OR PKT OR PAC OR DMA OR BIOL)/RL
L42 2 S L41 AND L35
L43 7 S L34,L40,L42
L44 2 S L24 AND BIOL+NT/RL AND L35
L45 7 S L43,L44
L46 7 S L45 AND L1-L8, L26-L45
L47 3 S L46 AND (PHARMACEUT? OR PHARMACOL?)/SC,SX
L48 6 S L46 AND L24(L) (THU OR BAC OR PKT OR PAC OR DMA OR BIOL)/RL
L49 7 S L46-L48

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L49 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:376963 HCAPLUS
DN 141:102080
ED Entered STN: 11 May 2004
TI Toward Better Antibiotics: Crystallographic Studies of a Novel Class of DD-Peptidase/ β -Lactamase Inhibitors
AU Silvaggi, Nicholas R.; Kaur, Kamaljit; Adediran, S. A.; Pratt, R. F.; Kelly, Judith A.
CS Department of Molecular and Cell Biology and Institute for Materials Science, University of Connecticut, Storrs, CT, 06269-3125, USA

SO Biochemistry (2004), 43(22), 7046-7053
CODEN: BICHAW; ISSN: 0006-2960

PB American Chemical Society

DT Journal

LA English

CC 7-3 (Enzymes)

Section cross-reference(s): 1

AB β -Lactam antibiotics are vital weapons in the treatment of bacterial infections, but their future is under increasing threat from **.beta** **.-lactamases**. These bacterial enzymes hydrolyze and inactivate β -lactam antibiotics, rendering the host cell resistant to the bactericidal effects of the drugs. Nevertheless, the bacterial D-alanyl-D-alanine transpeptidases (DD-peptidases), the killing targets of β -lactams, remain attractive targets for antibiotic compds. Cyclic acyl phosph(on)ates have been developed and investigated as potential inhibitors of both transpeptidases and β **-lactamases**. The x-ray crystal structures of the complexes of the Streptomyces strain R61 DD-peptidase inhibited by a bicyclic [1-hydroxy-4,5-benzo-2,6-dioxaphosphorinanone(3)-1-oxide] and a monocyclic [1-hydroxy-4-phenyl-2,6-dioxaphosphorinanone(3)-1-oxide] acyl phosphate were determined to investigate the mode of action of these novel inhibitors. The structures show, first, that these inhibitors form covalent bonds with the active site serine residue of the enzyme and that the refractory complexes thus formed are phosphoryl-enzyme species rather than acyl enzymes. The complexes are long-lived largely because, after ring opening, the ligands adopt conformations that cannot directly recyclize, the latter a phenomenon previously observed with cyclic acyl phosph(on)ates. While the two inhibitors bind in nearly identical conformations, the phosphoryl-enzyme complex formed from the monocyclic compound is significantly less mobile than that formed from the bicyclic compound. Despite this difference, the complex with the bicyclic compound breaks down to regenerate free enzyme somewhat more slowly than that of the monocyclic. This may be because of steric problems associated with the reorientation of the larger bicyclic ligand required for reactivation. The structures are strikingly different in the orientation of the phosphoryl moiety from those generated using more specific phosph(on)ates. Models of the noncovalent complexes of the monocyclic compound with the R61 DD-peptidase and a structurally very similar class C β **-lactamase** suggest reasons why the former enzyme is phosphorylated by this compound, while the latter is acylated. Finally, this paper provides information that will help in the design of addnl. DD-peptidase inhibitors with the potential to serve as leads in the development of novel antibiotics.

ST DD peptidase lactamase inhibitor crystal structure antibiotic design; dioxaphosphorinanone oxide inhibitor DD peptidase crystal structure

IT Enzyme functional sites
(active; crystal structure of DD-peptidase/ β **-lactamase** inhibitor complexes in relation to antibiotic design)

IT Chemical engineering design
(biochem. engineering design; crystal structure of DD-peptidase/ β **-lactamase** inhibitor complexes in relation to antibiotic design)

IT Conformation
Crystal structure
Molecular modeling
Streptomyces
(crystal structure of DD-peptidase/ β **-lactamase** inhibitor complexes in relation to antibiotic design)

IT Lactams
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β -, antibiotics; crystal structure of DD-peptidase/ β

-lactamase inhibitor complexes in relation to antibiotic design)

IT Antibiotics
(β -lactam; crystal structure of DD-peptidase/ β -
lactamase inhibitor complexes in relation to antibiotic design)

IT 56-45-1, L-Serine, biological studies 9073-60-3, β
-Lactamase 9077-67-2D, complexes with dioxaphosphorinanone
oxides
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(crystal structure of DD-peptidase/ β -lactamase
inhibitor complexes in relation to antibiotic design)

IT 91746-64-4D, complexes with DD-peptidase 717919-90-9D,
complexes with DD-peptidase
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(inhibitor; crystal structure of DD-peptidase/ β -
lactamase inhibitor complexes in relation to antibiotic design)

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

- (1) Anderson, J; Biochemistry 2000, V39, P12200 HCAPLUS
- (2) Bernstein, N; Biochemistry 1999, V38, P10499 HCAPLUS
- (3) Brunger, A; Acta Crystallogr, Sect D 1998, V54, P905
- (4) Bugg, T; Nat Prod Rep 1992, V9, P199 HCAPLUS
- (5) Bush, K; Antimicrob Agents Chemother 1989, V33, P259 HCAPLUS
- (6) Frere, J; Ann Biol Clin 1988, V46, P151 HCAPLUS
- (7) Frere, J; CRC Crit Rev Microbiol 1985, V11, P299 HCAPLUS
- (8) Ghuyssen, J; Microb Drug Resist 1996, V2, P163 HCAPLUS
- (9) Kaur, K; Biochemistry 2001, V40, P4610 HCAPLUS
- (10) Kaur, K; Biochemistry 2003, V42, P1529 HCAPLUS
- (11) Kaur, K; J Am Chem Soc 2001, V123, P10436 HCAPLUS
- (12) Kelly, J; J Mol Biol 1989, V209, P281 HCAPLUS
- (13) Kelly, J; J Mol Biol 1995, V254, P223 HCAPLUS
- (14) Kelly, J; Science 1986, V231, P1429 HCAPLUS
- (15) Knowles, J; Acc Chem Res 1985, V18, P97 HCAPLUS
- (16) Koch, A; Crit Rev Microbiol 2000, V26, P205 HCAPLUS
- (17) Kraulis, P; J Appl Crystallogr 1991, V24, P946
- (18) Kuzin, A; Biochemistry 1995, V34, P9532 HCAPLUS
- (19) Kuzmic, P; Anal Biochem 1996, V237, P260 HCAPLUS
- (20) Lee, W; Proc Natl Acad Sci U S A 2001, V98, P1427 HCAPLUS
- (21) Lobkovsky, E; Biochemistry 1994, V33, P6762 HCAPLUS
- (22) Lobkovsky, E; Proc Natl Acad Sci U S A 1993, V90, P11257 HCAPLUS
- (23) Massova, I; Antimicrob Agents Chemother 1998, V42, P1 HCAPLUS
- (24) McDonough, M; J Mol Biol 2002, V322, P111 HCAPLUS
- (25) McRee, D; J Struct Biol 1999, V125, P156 HCAPLUS
- (26) Meroueh, S; J Am Chem Soc 2003, V125, P9612 HCAPLUS
- (27) Merrit, E; Methods Enzymol 1997, V277, P505
- (28) Nugaka, M; J Biol Chem 1995, V270, P5729
- (29) Otwinowski, Z; Methods Enzymol 1997, V276, P307 HCAPLUS
- (30) Pratt, R; J Am Chem Soc 1998, V120, P3004 HCAPLUS
- (31) Pratt, R; J Chem Soc, Perkin Trans 2 2002, P851 HCAPLUS
- (32) Reading, C; Biochem J 1981, V199, P779 HCAPLUS
- (33) Sheldrick, G; Methods Enzymol 1997, V277, P319 HCAPLUS
- (34) Silvaggi, N; Biochemistry 2003, V42, P1199 HCAPLUS
- (35) Spratt, B; Bacterial Cell Wall 1994, P517 HCAPLUS
- (36) Tipper, D; Pharmacol Ther 1985, V27, P1 HCAPLUS
- (37) Tipper, D; Proc Natl Acad Sci U S A 1965, V54, P1133 HCAPLUS
- (38) Waley, S; The Chemistry of β -Lactams 1992, P198 HCAPLUS
- (39) Walsh, C; J Biol Chem 1989, V264, P2393 HCAPLUS
- (40) Waxman, D; Annu Rev Biochem 1983, V52, P825 HCAPLUS

OS CASREACT 138:233885

AB The cyclic acyl phosph(on)ates, 1-hydroxy-5-phenyl-2,6-dioxaphosphorinone(3)-1-oxide, its 4-Ph isomer, and the phosphonate (2-oxo) analog of the latter inhibited typical class A (TEM-2) and class C (Enterobacter cloacae P99) β -lactamases in a time-dependent fashion. No enzyme-catalyzed turnover was detected in any case. The interactions occurring were interpreted in terms of the reaction scheme $E + I \xrightarrow{k_1} EI \xrightarrow{k_{-1}} E + I$, where EI is a reversibly formed noncovalent complex, and EI' is a covalent complex. Reactions of the cyclic phosphates with the P99 β -lactamase were effectively irreversible, while that of the 4-Ph cyclic phosphate with the TEM β -lactamase was slowly reversible. The 4-Ph cyclic phosphate was generally the most effective inhibitor, both kinetically and thermodynamically, with second-order rate consts. of inactivation of both enzymes around $10^4 \text{ s}^{-1} \text{ M}^{-1}$. This compound also bound noncovalently to both enzymes, with dissociation consts. of $25 \mu\text{M}$ from the P99 enzyme and $100 \mu\text{M}$ from the TEM. It is unusual to find an inhibitor equally effective against the TEM and P99 enzymes; the β -lactamase inhibitors currently employed in medical practice (e.g., clavulanic acid) are significantly more effective against class A enzymes. The results of lysinoalanine anal. after hydroxide treatment of the inhibited enzymes and of a ^{31}P NMR spectrum of one such complex were interpreted as favoring a mechanism of inactivation by enzyme acylation rather than phosphorylation. Mol. modeling of the enzyme complexes of the 4-Ph phosphate revealed bound conformations where recyclization and thus reactivation of the enzyme would be difficult. The compds. studied were turned over slowly or not at all by acetylcholinesterase and phosphodiesterase I.

ST lactamase inactivation monocyclic acyl phosphate active site serine

IT Acylation

(P99 and TEM-2 β -lactamases can be inhibited by monocyclic acyl phosph(on)ates by acylation of serine residue at active site)

IT Enzyme functional sites

(inhibitor-binding; monocyclic acyl phosph(on)ates can acylate serine residue at active site of P99 and TEM-2 β -lactamase for its inhibition)

IT Enzyme kinetics

(of inhibition; kinetic parameters of P99 and TEM-2 β -lactamases)

IT 56-45-1, L-Serine, biological studies 9073-60-3, β -Lactamase 27238-11-5 91746-64-4 229344-36-9

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(P99 and TEM-2 β -lactamases can be inhibited by monocyclic acyl phosph(on)ates by acylation of serine residue at active site)

IT 501948-95-4P 501948-97-6P

RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(P99 and TEM-2 β -lactamases can be inhibited by monocyclic acyl phosph(on)ates by acylation of serine residue at active site)

IT 90-27-7, 2-Phenyl butanoic acid 101-97-3, Ethyl phenylacetate 109-94-4, Ethyl formate 119-43-7, Ethyl 2-phenyl butanoate 122-52-1 128-08-5, N-Bromosuccinimide 814-49-3

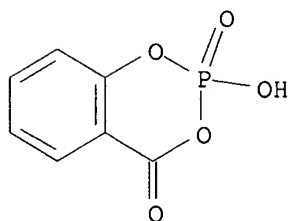
RL: RCT (Reactant); RACT (Reactant or reagent)

(P99 and TEM-2 β -lactamases can be inhibited by monocyclic acyl phosph(on)ates by acylation of serine residue at active site)

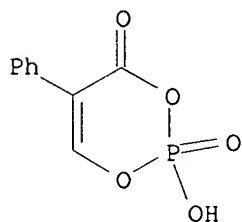
IT 9073-60-3, β -Lactamase
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(crystal structure of DD-peptidase/ β -lactamase
inhibitor complexes in relation to antibiotic design)
RN 9073-60-3 HCAPLUS
CN Lactamase, β - (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 91746-64-4D, complexes with DD-peptidase 717919-90-9D,
complexes with DD-peptidase
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(inhibitor; crystal structure of DD-peptidase/ β -
lactamase inhibitor complexes in relation to antibiotic design)
RN 91746-64-4 HCAPLUS
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX
NAME)



RN 717919-90-9 HCAPLUS
CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-5-phenyl-, 2-oxide (9CI) (CA
INDEX NAME)



L49 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:55270 HCAPLUS
DN 138:233885
ED Entered STN: 24 Jan 2003
TI Inhibition of β -Lactamases by Monocyclic Acyl
Phosph(on)ates
AU Kaur, Kamaljit; Adediran, S. A.; Lan, Martin J. K.; Pratt, R. F.
CS Department of Chemistry, Wesleyan University, Middletown, CT, 06459, USA
SO Biochemistry (2003), 42(6), 1529-1536
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 7-3 (Enzymes)

IT 17838-69-6P, Ethyl 2-formyl-2-phenylacetate 40233-96-3P 501948-98-7P
501948-99-8P 501949-00-4P 501949-01-5P 501949-02-6P 501949-03-7P
501949-04-8P 501949-05-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(P99 and TEM-2 β -lactamases can be inhibited
by monocyclic acyl phosph(on)ates by acylation of serine residue at
active site)

IT 9000-81-1, Acetylcholinesterase 9025-82-5, Phosphodiesterase I
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(monocyclic acyl phosph(on)ates do not inhibit acetylcholinesterase and
phosphodiesterase I)

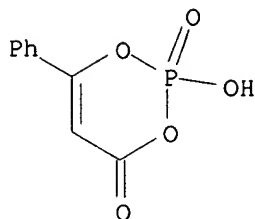
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Becalli, E; J Org Chem 1984, V49, P4287
(2) Breukelman, S; J Chem Soc Perkin Trans I 1995, P1627
(3) Buynak, J; Bioorg Med Chem Lett 2002, V10, P853
(4) Chen, C; J Mol Biol 1993, V224, P1103
(5) Craig, J; J Chem Soc 1963, P3712
(6) Crichlow, G; Biochemistry 2001, V40, P6233 HCAPLUS
(7) Curley, K; J Am Chem Soc 1997, V119, P1529 HCAPLUS
(8) Gordon, E; J Mol Biol 2000, V299, P477 HCAPLUS
(9) Hays, H; J Org Chem 1971, V36, P98 HCAPLUS
(10) Hudson, R; J Chem Soc 1960, P1859 HCAPLUS
(11) Ishii, H; J Chem Soc Perkin Trans I 1985, P2353 HCAPLUS
(12) Jelsch, C; Proteins:Struct Funct Genetics 1993, V16, P364 HCAPLUS
(13) Kaur, K; Biochemistry 2001, V40, P4610 HCAPLUS
(14) Kaur, K; J Am Chem Soc 2001, V43, P10436
(15) Kuzin, A; Biochemistry 1995, V34, P9532 HCAPLUS
(16) Kuzmic, P; Anal Biochem 1996, V237, P260 HCAPLUS
(17) Li, N; Bioorg Med Chem 1997, V5, P1783 HCAPLUS
(18) Li, N; J Am Chem Soc 1998, V120, P4264 HCAPLUS
(19) Lobkovsky, E; Biochemistry 1994, V33, P6762 HCAPLUS
(20) Lobkovsky, E; Proc Natl Acad Sci U S A 1993, V90, P11257 HCAPLUS
(21) Marecek, J; J Am Chem Soc 1970, V92, P917 HCAPLUS
(22) Maveyraud, L; Biochemistry 1997, V38, P2622
(23) Miller, L; Curr Opin Pharmacol 2001, V1, P451 HCAPLUS
(24) Oefner, C; Nature 1990, V343, P284 HCAPLUS
(25) Page, M; Adv Phys Org Chem 1987, V23, P165 HCAPLUS
(26) Page, M; Drug Resist Updates 2000, V3, P109 HCAPLUS
(27) Patera, A; J Am Chem Soc 2000, V122, P10504 HCAPLUS
(28) Pratt, R; J Am Chem Soc 1998, V120, P3004 HCAPLUS
(29) Pratt, R; J Chem Soc Perkin Trans 2 2002, P851 HCAPLUS
(30) Rahil, J; Biochemistry 1992, V31, P5869 HCAPLUS
(31) Rahil, J; Biochemistry 1994, V33, P116 HCAPLUS
(32) Reich, H; J Am Chem Soc 1973, V95, P5813 HCAPLUS
(33) Schauble, J; J Org Chem 1974, V39, P755 HCAPLUS
(34) Slougui, N; Synth Commun 1982, V12, P401 HCAPLUS
(35) Strynadka, N; Nature 1992, V359, P700 HCAPLUS

IT 9073-60-3, β -Lactamase 27238-11-5
91746-64-4 229344-36-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(P99 and TEM-2 β -lactamases can be inhibited
by monocyclic acyl phosph(on)ates by acylation of serine residue at
active site)

RN 9073-60-3 HCAPLUS
CN Lactamase, β - (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 27238-11-5 HCAPLUS

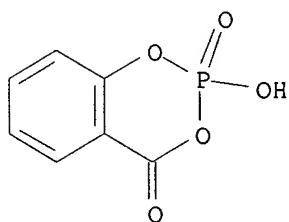
CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide, sodium salt
(9CI) (CA INDEX NAME)



● Na

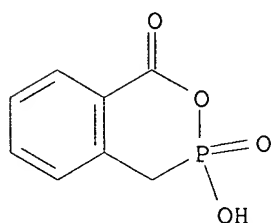
RN 91746-64-4 HCAPLUS

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



RN 229344-36-9 HCAPLUS

CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)



IT 501948-95-4P 501948-97-6P

RL: BSU (Biological study, unclassified); SPN (Synthetic preparation);

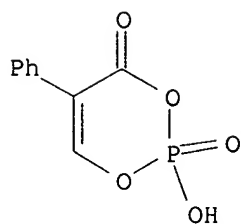
BIOL (Biological study); PREP (Preparation)

(P99 and TEM-2 β -lactamases can be inhibited

by monocyclic acyl phosph(on)ates by acylation of serine residue at active site)

RN 501948-95-4 HCAPLUS

CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-5-phenyl-, 2-oxide, sodium salt
(9CI) (CA INDEX NAME)

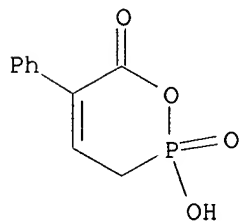


● Na

RN 501948-97-6 HCAPLUS
 CN 6H-1,2-Oxaphosphorin-6-one, 2,3-dihydro-2-hydroxy-5-phenyl-, 2-oxide,
 compd. with N-cyclohexylcyclohexanamine (1:1) (9CI) (CA INDEX NAME)

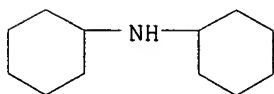
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CRN 501948-96-5
 CMF C10 H9 O4 P



CM 2

CRN 101-83-7
 CMF C12 H23 N



L49 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2002:143282 HCAPLUS
 DN 136:183941
 ED Entered STN: 22 Feb 2002
 TI Preparation of acyl phosphate and acyl phosphonate derivatives as
 inhibitors of **beta-lactamases** and DD-peptidases
 IN **Besterman, Jeffrey M.; Rahil, Jubrail; Pratt,**
Rex
 PA Can.
 SO U.S. Pat. Appl. Publ., 30 pp., Cont.-in-part of U.S. Ser. No. 582,255.
 CODEN: USXXCO

DT Patent
 LA English
 IC ICM C07F009-547
 ICS C07F009-141; A61K031-66
 INCL 514105000
 CC 29-7 (Organometallic and Organometalloidal Compounds)
 Section cross-reference(s): 1, 7, 10, 63

FAN.CNT 2

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PI	US 2002022607	A1	20020221	US 2001-797308	20010301 <--
	US 6599889	B2	20030729		
	WO 9933850	A1	19990708	WO 1998-US27518	19981223 <--
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	US 2005119233	A1	20050602	US 2003-628649	20030728 <--
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	WO 1998-US27518	W	19981223	<--	
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	US 2001-797308	A3	20010301	<--	

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	INCL	514105000
US 2002022607	NCL	514/105.000
	ECLA	C07F009/09A9Q; C07F009/09B; C07F009/40C9Q; C07F009/6571L4; C07F009/6574A4; C07F009/6574A1 <--
WO 9933850	ECLA	C07F009/09A9Q; C07F009/09B; C07F009/40C9Q; C07F009/6571L4; C07F009/6574A1; C07F009/6574A4 <--
US 6608046	NCL	514/120.000; 423/302.000; 423/316.000; 558/079.000; 568/012.000
	ECLA	C07F009/09A9Q; C07F009/09B; C07F009/40C9Q; C07F009/6571L4; C07F009/6574A4; C07F009/6574A1 <--
US 2005119233	NCL	514/124.000
	ECLA	C07F009/09A9Q; C07F009/09B; C07F009/40C9Q; C07F009/6571L4; C07F009/6574A1; C07F009/6574A4 <--

OS MARPAT 136:183941

AB Acyl phosphates and acyl phosphonates, e.g. sodium benzoyl Ph phosphate (I), were prepared Thus, disodium Ph phosphate was reacted with benzoic anhydride to give I. The prepared compds. bind bacterial DD-peptidases, thus potentially acting both as β -lactamase inhibitors and as antibiotics. Biol. data are given.

ST lactamase inhibitor phosphonate phosphate prepn; antibiotic phosphonate phosphate prepn lactamase peptidase inhibitor; peptidase inhibitor phosphonate phosphate prepn; phosphonate prepn lactamase peptidase inhibitor; phosphate prepn lactamase peptidase inhibitor; antibacterial phosphonate phosphate prepn **beta lactamase** inhibitor

IT Antibacterial agents
 Antibiotic resistance
 Antibiotics
 Human

(preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

IT 9073-60-3 9077-67-2
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (inhibitors; preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

IT 50363-66-1P 68977-60-6P 91746-64-4P 91929-16-7P
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 341554-86-7P 341554-87-8P 341554-88-9P 341554-89-0P 341554-90-3P
 383914-12-3P 383914-14-5P 400605-07-4P 400605-09-6P
 400605-11-0P 400605-14-3P 400605-16-5P 400605-18-7P 400605-21-2P
 400605-23-4P 400605-25-6P 400605-27-8P 400605-29-0P
 400605-31-4P 400605-32-5P 400605-34-7P 400605-36-9P 400605-42-7P
 400605-43-8P 400605-44-9P 400605-47-2P 400605-69-8P
 400605-71-2P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation);
 THU (Therapeutic use); BIOL (Biological study); PREP
 (Preparation); USES (Uses)
 (preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

IT 69-72-7, Salicylic acid, reactions 77-98-5, Tetraethylammonium hydroxide
 93-97-0, Benzoic anhydride 98-88-4, Benzoyl chloride 500-98-1,
 Phenylacetyl glycine 770-12-7, Phenyl dichlorophosphate 3279-54-7
 7558-79-4, Disodium hydrogenphosphate 10025-87-3, Phosphorus oxychloride
 55601-40-6
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

IT 383914-15-6P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

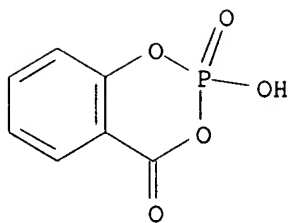
IT 9073-60-3
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (inhibitors; preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

RN 9073-60-3 HCAPLUS
 CN Lactamase, β - (9CI) (CA INDEX NAME)

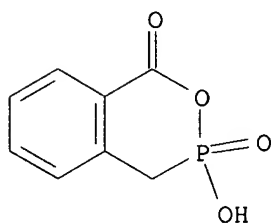
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 RL: PAC (Pharmacological activity); SPN (Synthetic preparation);
 THU (Therapeutic use); BIOL (Biological study); PREP
 (Preparation); USES (Uses)
 (preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

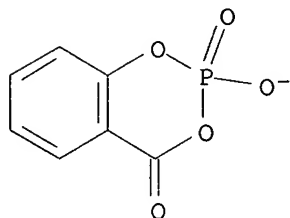
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 CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



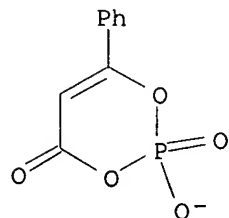
RN 229344-36-9 HCAPLUS
 CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)



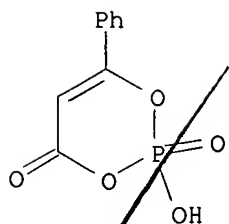
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 CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide, ion(1-) (9CI) (CA INDEX NAME)



RN 400605-23-4 HCAPLUS
 CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide, ion(1-) (9CI) (CA INDEX NAME)



RN 400605-71-2 HCAPLUS
 CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide (9CI) (CA INDEX NAME)



149 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2001:731840 HCAPLUS

DN 136:33785

ED Entered STN: 08 Oct 2001

TI Mechanism of Inhibition of the Class C β -Lactamase
of Enterobacter cloacae P99 by Cyclic Acyl Phosph(on)ates: Rescue by
Return

AU Kaur, Kamaljit; Lan, Martin J. K.; Pratt, R. F.

CS Department of Chemistry, Wesleyan University, Middletown, CT, 06459, USA

SO Journal of the American Chemical Society (2001), 123(43), 10436-10443

CODEN: JACSAT; ISSN: 0002-7863

PB American Chemical Society

DT Journal

LA English

CC 7-4 (Enzymes)

OS CASREACT 136:33785

AB As previously described (Pratt, R. F.; Hammar, N. J. J. Am. Chemical Society 1998, 120, 3004.), 1-hydroxy-4,5-benzo-2,6-dioxaphosphorinone(3)-1-oxide (salicyloyl cyclic phosphate) inactivates the class C β -lactamase of Enterobacter cloacae P99 in a covalent fashion. The inactivated enzyme slowly reverts to the active form. This paper shows that reactivation involves a recyclization reaction that regenerates salicyloyl cyclic phosphate rather than hydrolysis of the covalent intermediate. The inactivation, therefore, is a slowly reversible covalent modification of the active site. The thermodyn. dissociation constant of the inhibitor from the inactivated enzyme is 0.16 μ M. Treatment of the inactivated enzyme with alkali does not produce salicylic acid but does, after subsequent acid hydrolysis, yield one molar equivalent of lysinoalanine. This result proves that salicyloyl cyclic phosphate inactivates the enzyme by (slowly reversible) phosphorylation of the active site serine residue. This result contrasts sharply with the behavior of acyclic acyl phosphates which transiently inactivate the P99 β -lactamase by acylation (Li, N.; Pratt, R. F. J. Am. Chemical Society 1998, 120, 4264.). This chemoselectivity difference is explored by means of mol. modeling. Rather counterintuitively, in view of the relative susceptibility of phosphates and phosphonates to nucleophilic attack at phosphorus, 1-hydroxy-4,5-benzo-2-oxaphosphorinanone(3)-1-oxide, the phosphonate analog of salicyloyl cyclic phosphate, did not appear to inactivate the P99 β -lactamase in a time-dependent fashion. It was found, however, to act as a fast reversible inhibitor ($K_i = 10 \mu$ M). A closer examination of the kinetics of inhibition revealed that both on and off rates ($9.8 \pm 103 \text{ s}^{-1} \text{ M}^{-1}$ and 0.098 s^{-1} , resp.) were much slower than expected for noncovalent binding. This result strongly indicates that the inhibition reaction of the phosphonate also involves phosphorylation of the active site. Hence, unlike the situation with bacterial DD-peptidases covalently inactivated by β -lactams, the P99 β -lactamase inactivated by the above cyclic acyl phosph(on)ates can be rescued by

return. Elimination of the recyclization reaction would lead to more effective inhibitors.

ST lactamase Enterobacter inhibition cyclic phosphonate; phosphate cyclic phosphorylation serine Enterobacter lactamase

IT Enterobacter cloacae
Enzyme functional sites
(cyclic acyl phosphates and phosphonates inhibit class C β -lactamase from E. cloacae P99 by reversible phosphorylation of active site serine)

IT Enzyme kinetics
(of inhibition; cyclic acyl phosphates and phosphonates inhibit class C β -lactamase from E. cloacae P99 by reversible phosphorylation of active site serine)

IT 56-45-1, L-Serine, biological studies 9073-60-3, β -Lactamase 91746-64-4 109099-32-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cyclic acyl phosphates and phosphonates inhibit class C β -lactamase from E. cloacae P99 by reversible phosphorylation of active site serine)

IT 229344-36-9P 379699-46-4P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(cyclic acyl phosphates and phosphonates inhibit class C β -lactamase from E. cloacae P99 by reversible phosphorylation of active site serine)

IT 87-24-1 98-88-4, Benzoyl chloride 122-52-1, Triethyl phosphite 128-08-5, N-Bromosuccinimide 6881-57-8, Benzylphosphonic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyclic acyl phosphates and phosphonates inhibit class C β -lactamase from E. cloacae P99 by reversible phosphorylation of active site serine)

IT 7115-91-5P 79026-11-2P 101259-28-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(cyclic acyl phosphates and phosphonates inhibit class C β -lactamase from E. cloacae P99 by reversible phosphorylation of active site serine)

IT 850423-14-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(cyclic acyl phosphates and phosphonates inhibit class C β -lactamase from E. cloacae P99 by reversible phosphorylation of active site serine)

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Abraham, E; Nature 1940, V146, P837 HCAPLUS
- (2) Besterman, J; 1999 HCAPLUS
- (3) Campbell, P; Biochem Biophys Res Commun 1972, V48, P866 HCAPLUS
- (4) Cleland, W; Methods Enzymol 1979, V63, P103 HCAPLUS
- (5) Curley, K; J Am Chem Soc 1997, V119, P1529 HCAPLUS
- (6) Disabato, G; J Am Chem Soc 1961, V83, P4400 HCAPLUS
- (7) Eftink, M; Hydrolytic Enzymes, Chapter 7 1987
- (8) Frere, J; Crit Rev Microbiol 1985, V11, P299 HCAPLUS
- (9) Garuti, L; Pharmazie 1992, V47, P295 MEDLINE
- (10) Gordon, E; J Mol Biol 2000, V299, P477 HCAPLUS
- (11) Hays, H; J Org Chem 1971, V36, P98 HCAPLUS
- (12) Hedstrom, L; Biochemistry 1984, V23, P1753 HCAPLUS
- (13) Heidema, J; J Am Chem Soc 1970, V92, P6050 HCAPLUS
- (14) Hudson, R; J Chem Soc 1960, P1859 HCAPLUS
- (15) Kaur, K; Biochemistry 2001, V40, P4610 HCAPLUS
- (16) Kirby, W; Science 1944, V99, P452 HCAPLUS

- (17) Kuzin, A; Biochemistry 1995, V34, P9532 HCAPLUS
- (18) Kuzmic, P; Anal Biochem 1996, V237, P260 HCAPLUS
- (19) Li, N; J Am Chem Soc 1998, V120, P4264 HCAPLUS
- (20) Lobkovsky, E; Biochemistry 1994, V33, P6762 HCAPLUS
- (21) Medeiros, A; Clin Infect Dis 1997, V24(Suppl 1), P519
- (22) Page, M; Adv Phys Org Chem 1987, V23, P165 HCAPLUS
- (23) Pratt, R; J Am Chem Soc 1998, V120, P3004 HCAPLUS
- (24) Pratt, R; Science 1989, V246, P917 HCAPLUS
- (25) Pratt, R; The Chemistry of β -Lactams 1992, P229 HCAPLUS
- (26) Rahil, J; Biochem J 1993, V296, P389 HCAPLUS
- (27) Rahil, J; Biochemistry 1992, V31, P5869 HCAPLUS
- (28) Rice, L; Drug Resist Updates 2000, V3, P178 HCAPLUS
- (29) Weir, M; Biochemistry 1998, V37, P6645 HCAPLUS
- (30) Weston, G; J Med Chem 1998, V41, P4577 HCAPLUS

IT 9073-60-3, β -Lactamase 91746-64-4

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (cyclic acyl phosphates and phosphonates inhibit class C β -
 -lactamase from *E. cloacae* P99 by reversible phosphorylation
 of active site serine)

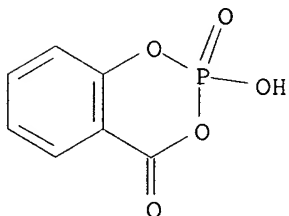
RN 9073-60-3 HCAPLUS

CN Lactamase, β - (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)

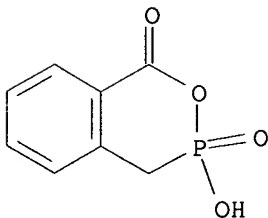


IT 229344-36-9P

RL: BSU (Biological study, unclassified); SPN (Synthetic preparation);
 BIOL (Biological study); PREP (Preparation)
 (cyclic acyl phosphates and phosphonates inhibit class C β -
 -lactamase from *E. cloacae* P99 by reversible phosphorylation
 of active site serine)

RN 229344-36-9 HCAPLUS

CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)



IT 850423-14-2P

RL: SPN (Synthetic preparation); PREP (Preparation)
 (cyclic acyl phosphates and phosphonates inhibit class C β -lactamase from *E. cloacae* P99 by reversible phosphorylation of active site serine)

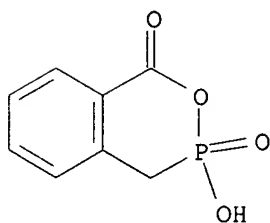
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CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide, compd. with N-cyclohexylcyclohexanamine (1:1) (9CI) (CA INDEX NAME)

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CRN 229344-36-9

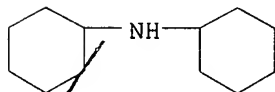
CMF C8 H7 O4 P



CM 2

CRN 101-83-7

CMF C12 H23 N



L49 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1999:460434 HCAPLUS

DN 131:82947

ED Entered STN: 28 Jul 1999

TI Novel β -lactamase and DD-peptidase inhibitors

IN Besterman, Jeffrey M.; Rahil, Jubrail; Pratt, Rex

PA Methylgene, Inc., Can.; Wesleyan University

SO PCT Int. Appl., 47 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07F009-40

ICS A61K031-66; C07F009-6574; C07F009-6571; C07F009-09

CC 1-5 (Pharmacology)

Section cross-reference(s): 7, 10, 29

FAN.CNT 2

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 MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
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 FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
 CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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 IE, FI

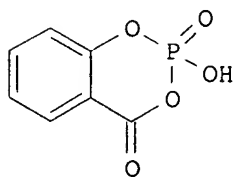
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CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
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WO 9933850	ECLA	C07F009/09A9Q; C07F009/09B; C07F009/40C9Q; C07F009/6571L4; C07F009/6574A1; C07F009/6574A4 <--
US 6608046	NCL	514/120.000; 423/302.000; 423/316.000; 558/079.000; 568/012.000
	ECLA	C07F009/09A9Q; C07F009/09B; C07F009/40C9Q; C07F009/6571L4; C07F009/6574A4; C07F009/6574A1 <--
US 2002022607	NCL	514/105.000
	ECLA	C07F009/09A9Q; C07F009/09B; C07F009/40C9Q; C07F009/6571L4; C07F009/6574A4; C07F009/6574A1 <--
US 2005119233	NCL	514/124.000
	ECLA	C07F009/09A9Q; C07F009/09B; C07F009/40C9Q; C07F009/6571L4; C07F009/6574A1; C07F009/6574A4 <--

OS MARPAT 131:82947
 GI



I

AB The invention provides novel β -lactamase inhibitors, which are structurally unrelated to the natural product and semi-synthetic β -lactamase inhibitors presently available, and which do not possess β -lactam pharmacophore. These new inhibitors are fully synthetic, allowing ready access to a wide variety of structurally related analogs. The inhibitors also bind

bacterial DD-peptidases, thus potentially acting both a β -
lactamase inhibitors and as antibiotics. β -
Lactamase inhibition by the compds. and compds. such as I and
PhCO₂P(O)(O-)Me may have antibiotic properties, as evidenced by their
inhibition of DD-peptidase.

ST phosphate lactamase peptidase inhibitor; phosphonate lactamase peptidase
inhibitor; lactamase inhibitor phosphonate phosphate; peptidase inhibitor
phosphonate phosphate

IT Antibiotic resistance
Antibiotics
(phosphate and phosphonate β -**lactamase** and
DD-peptidase inhibitors)

IT 9073-60-3, β -**Lactamase** 9077-67-2
RL: BPR (Biological process); BSU (Biological study,
unclassified); BIOL (Biological study); PROC (Process)
(inhibitors; phosphate and phosphonate β -
lactamase and DD-peptidase inhibitors)

IT 50363-66-1P 91746-64-4P 91929-16-7P 109099-32-3P
229344-36-9P 229344-37-0P 229344-38-1P 229344-39-2P
229344-40-5P 229344-41-6P 229344-42-7P 229344-43-8P
229344-44-9P
RL: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); SPN (Synthetic preparation);
THU (Therapeutic use); BIOL (Biological study); PREP
(Preparation); USES (Uses)
(phosphate and phosphonate β -**lactamase** and
DD-peptidase inhibitors)

IT 69-72-7, reactions 93-97-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(phosphate and phosphonate β -**lactamase** and
DD-peptidase inhibitors)

IT 5381-98-6P 83868-01-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(phosphate and phosphonate β -**lactamase** and
DD-peptidase inhibitors)

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Kazlauskas, R; J ORG CHEM 1985, V50(7), P1069 HCAPLUS
(2) Laird, R; J CHEM SOC PERKIN TRANS 1973, V2(10), P1434
(3) Li, N; BIOORG MED CHEM 1997, V5(9), P1783 HCAPLUS
(4) Li, N; JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 1998, V120(18), P4264
HCAPLUS
(5) Pratt, R; JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 1998, V120(13), P3004
HCAPLUS
(6) Rahil, J; BIOCHEM J 1991, V275(3), P793 HCAPLUS
(7) Song, Y; BIOORG MED CHEM LETT 1994, V4(10), P1225 HCAPLUS

IT 9073-60-3, β -**Lactamase**
RL: BPR (Biological process); BSU (Biological study,
unclassified); BIOL (Biological study); PROC (Process)
(inhibitors; phosphate and phosphonate β -
lactamase and DD-peptidase inhibitors)

RN 9073-60-3 HCAPLUS

CN Lactamase, β - (9CI) (CA INDEX NAME)

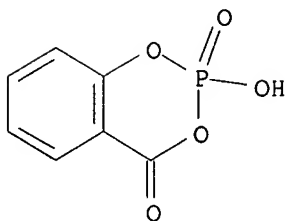
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 91746-64-4P 229344-36-9P 229344-44-9P
RL: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); SPN (Synthetic preparation);
THU (Therapeutic use); BIOL (Biological study); PREP

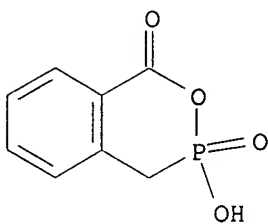
(Preparation); USES (Uses)

(phosphate and phosphonate β -lactamase and
DD-peptidase inhibitors)

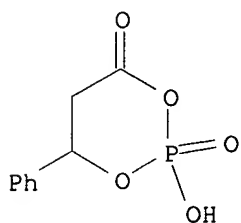
RN 91746-64-4 HCAPLUS

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX
NAME)

RN 229344-36-9 HCAPLUS

CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA
INDEX NAME)

RN 229344-44-9 HCAPLUS

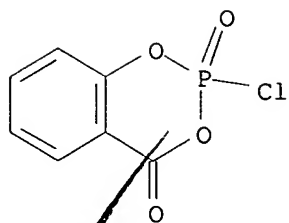
CN 1,3,2-Dioxaphosphorinan-4-one, 2-hydroxy-6-phenyl-, 2-oxide (9CI) (CA
INDEX NAME)

IT 5381-98-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)(phosphate and phosphonate β -lactamase and
DD-peptidase inhibitors)

RN 5381-98-6 HCAPLUS

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-chloro-, 2-oxide (9CI) (CA INDEX
NAME)



L49 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1998:178951 HCAPLUS
 DN 128:305512
 ED Entered STN: 27 Mar 1998
 TI Salicyloyl Cyclic Phosphate, a "Penicillin-Like" Inhibitor of .
beta.-Lactamases
 AU Pratt, R. F.; Hammar, Ned J.
 CS Chemistry Department, Wesleyan University, Middletown, CT, 06459, USA
 SO Journal of the American Chemical Society (1998), 120(13), 3004-3006
 CODEN: JACSAT; ISSN: 0002-7863
 PB American Chemical Society
 DT Journal
 LA English
 CC 7-3 (Enzymes)
 AB Salicyloyl cyclic phosphate (1-hydroxy-4,5-benzo-2,6-dioxaphosphorinane (3)-1-oxide) was designed as a "penicillin-like" inhibitor of .
beta.-lactamases. It was anticipated that, after nucleophilic attack on this mol. by the enzyme, the leaving group would remain tethered, and, as in the inhibition of DD-peptidases by penicillins, obstruct hydrolysis of the covalent intermediate back to free enzyme. The target mol., hitherto only reported as a transient intermediate, was prepared by hydrolysis of the cognate cyclic phosphoryl chloride and isolated and characterized as the dicyclohexylammonium salt. It proved to transiently inhibit the class C β -**lactamase** of *Enterobacter cloacae* P99, the class A TEM .
beta.-lactamase, and also the DD-peptidase of *Streptomyces* R61. Most significantly, the half-lives of the complexes formed with these enzymes were 14, 140, and 340 min, resp. Thus, this cyclic phosphate represents a new class of mol. leading to inert complexes of β -lactam-recognizing enzymes.
 ST prepn salicyloyl phosphate inhibitor **beta lactamase**
 IT Enzyme kinetics
 (of inhibition; preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β -**lactamases**)
 IT 91746-64-4P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β -**lactamases**)
 IT 9073-60-3, β -**Lactamase** 9077-67-2
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β -**lactamases**)
 IT 5381-98-6
 RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β -lactamases)

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

- (1) Bender, M; J Am Chem Soc 1963, V85, P3010 HCAPLUS
- (2) Bruice, T; J Am Chem Soc 1995, V117, P12064 HCAPLUS
- (3) Courvalin, P; J Antimicrob Chemother 1996, V37, P855 HCAPLUS
- (4) Cremllyn, R; Phosphorus Sulfur 1980, V10, P333
- (5) Davies, J; Nature 1996, V383, P219 HCAPLUS
- (6) Govardhan, C; Biochemistry 1987, V26, P3385 HCAPLUS
- (7) Johnson, M; Biochemistry 1976, V15, P5363 HCAPLUS
- (8) Li, N; Biorg Med Chem 1997, V5, P1783 HCAPLUS
- (9) Medeiros, A; Clin Infect Dis 1997, V24(Suppl 1), PS19
- (10) Montgomery, H; J Chem Soc 1956, P4603 HCAPLUS
- (11) Neu, H; Science 1992, V257, P1064 HCAPLUS
- (12) Pazhanisamy, S; Biochemistry 1989, V28, P6870 HCAPLUS
- (13) Pratt, R; Science 1989, V246, P917 HCAPLUS
- (14) Pratt, R; The Chemistry of β -Lactams 1992, P229 HCAPLUS
- (15) Rahil, J; Biochem J 1991, V275, P793 HCAPLUS
- (16) Rahil, J; Biochem J 1993, V296, P389 HCAPLUS
- (17) Rahil, J; Biochemistry 1992, V31, P5869 HCAPLUS
- (18) Xu, Y; Biochemistry 1996, V35, P3595 HCAPLUS
- (19) Zimmerle, C; Biochem J 1989, V258, P381 HCAPLUS

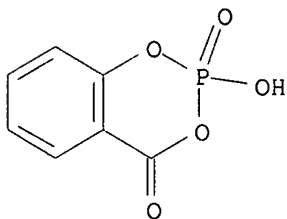
IT 91746-64-4P

RL: BAC (Biological activity or effector, except adverse); BSU
(Biological study, unclassified); SPN (Synthetic preparation); BIOL
(Biological study); PREP (Preparation)

(preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β -lactamases)

RN 91746-64-4 HCAPLUS

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



IT 9073-60-3, β -Lactamase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)

(preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β -lactamases)

RN 9073-60-3 HCAPLUS

CN Lactamase, β - (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

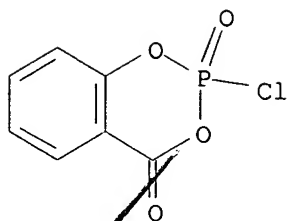
IT 5381-98-6

RL: RCT (Reactant); RACT (Reactant or reagent)

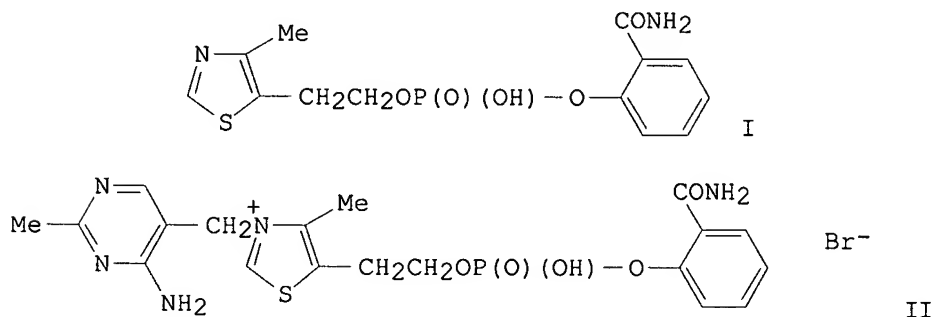
(preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β -lactamases)

RN 5381-98-6 HCAPLUS

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-chloro-, 2-oxide (9CI) (CA INDEX NAME)



L49 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1981:619996 HCAPLUS
 DN 95:219996
 ED Entered STN: 12 May 1984
 TI Synthesis of the o-carbamoylphenyl ester of thiamine monophosphate
 AU Lettieri, G.; Brancaccio, G.; Larizza, A.; Viterbo, R.
 CS Lab. Ric., Richardson-Merrell S.p.A., Naples, Italy
 SO Bollettino Chimico Farmaceutico (1981), 120(5), 303-7
 CODEN: BCFAAI; ISSN: 0006-6648
 DT Journal
 LA Italian
 CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
 Section cross-reference(s): 1
 GI



AB The thiazoleethanol ester I was converted to the title thiamine derivative (II). A mixture of I cyclohexylammonium salt, 2-methyl-4-amino-5-(bromomethyl)pyrimidine hydrobromide, and CHBr3 was stirred at 105° to give II, useful as an analgesic and antiinflammatory agent (no data).
 ST thiamine phenylphosphate prepn analgesic; antiinflammatory thiamine phenylphosphate prepn
 IT Analgesics
 Inflammation inhibitors
 (thiamine monophosphate derivative)
 IT 7664-41-7, reactions
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (amidation of O-(o-carboxyphenyl) phosphoric acid derivative by)
 IT 2908-71-6
 RL: PROC (Process)
 (conversion of, to thiamine derivative)

IT 137-00-8
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (esterification of O-(o-carboxyphenyl) phosphoric acid derivative by)

IT 5381-98-6
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (esterification of, by (hydroxyethyl)thiazole derivative)

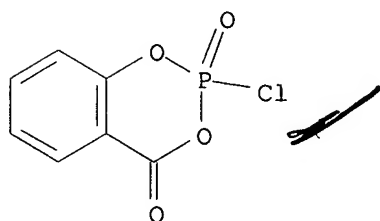
IT 79929-26-3P 79929-27-4P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation and conversion of, to thiamine derivative)

IT 79929-28-5P 79929-29-6P 79929-30-9P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of)

IT 5381-98-6
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (esterification of, by (hydroxyethyl)thiazole derivative)

RN 5381-98-6 HCAPLUS

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-chloro-, 2-oxide (9CI) (CA INDEX NAME)



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FILE 'USPATFULL' ENTERED AT 08:22:23 ON 08 DEC 2005
 CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 08:22:23 ON 08 DEC 2005
 CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

=> d his 150-

(FILE 'USPATFULL, USPAT2' ENTERED AT 08:21:54 ON 08 DEC 2005)

L50 4 S L24
 L51 4 S L50 AND A61K/IPC

FILE 'USPATFULL, USPAT2' ENTERED AT 08:22:23 ON 08 DEC 2005

=> d bib abs hitstr tot

L51 ANSWER 1 OF 4 USPATFULL on STN
 AN 2005:138583 USPATFULL
 TI Acyl phosphonate inhibitors of beta-lactamases
 IN Besterman, Jeffrey M., Baie D'Urfe, CANADA
 Rahil, Jubrail, Dollard Des Ormeaux, CANADA
 Pratt, Rex, Portland, CT, UNITED STATES
 PI US 2005119233 A1 20050602
 AI US 2003-628649 A1 20030728 (10)
 RLI Division of Ser. No. US 2001-797308, filed on 1 Mar 2001, GRANTED, Pat.
 No. US 6599889 Continuation-in-part of Ser. No. US 2000-582255, filed on
 1 Sep 2000, GRANTED, Pat. No. US 6608046 A 371 of International Ser. No.

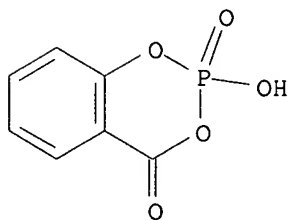
WO 1998-US27518, filed on 23 Dec 1998
 PRAI US 1997-68837P 19971224 (60)
 DT Utility
 FS APPLICATION
 LREP KEOWN & ASSOCIATES, 500 WEST CUMMINGS PARK, SUITE 1200, WOBURN, MA,
 01801, US
 CLMN Number of Claims: 50
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 1228

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

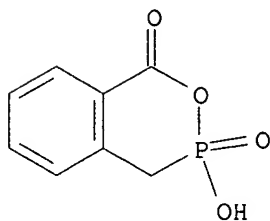
AB The invention provides novel β -lactamase inhibitors, which are structurally unrelated to the natural product and semi-synthetic β -lactamase inhibitors presently available, and which do not possess a β -lactam pharmacophore. These new inhibitors are fully synthetic, allowing ready access to a wide variety of structurally related analogs. Certain embodiments of these new inhibitors also bind bacterial DD-peptidases, thus potentially acting both as β -lactamase inhibitors and as antibiotics.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

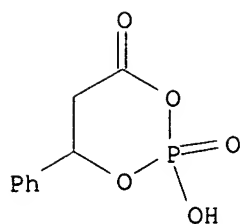
IT 91746-64-4P 229344-36-9P 229344-44-9P
 (phosphate and phosphonate β -lactamase and DD-peptidase inhibitors)
 RN 91746-64-4 USPATFULL
 CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



RN 229344-36-9 USPATFULL
 CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)



RN 229344-44-9 USPATFULL
 CN 1,3,2-Dioxaphosphorinan-4-one, 2-hydroxy-6-phenyl-, 2-oxide (9CI) (CA INDEX NAME)

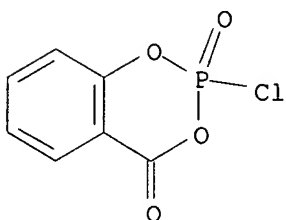


IT 5381-98-6P

(phosphate and phosphonate β -lactamase and DD-peptidase inhibitors)

RN 5381-98-6 USPATFULL

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-chloro-, 2-oxide (9CI) (CA INDEX NAME)



L51 ANSWER 2 OF 4 USPATFULL on STN

AN 2003:222100 USPATFULL

TI β -lactamase and DD-peptidase inhibitors

IN Besterman, Jeffrey M., Baie d'Urfe, CANADA

Rahil, Jubrail, Dollard des Ormeaux, CANADA

Pratt, Rex, Portland, CT, United States

PA MethylGene, Inc., St. Laurent, CANADA (non-U.S. corporation)

PI US 6608046 B1 20030819

WO 9933850 19990708

AI US 2000-582255 20000901 (9)

WO 1998-US27518 19981223

PRAI US 1997-68837P 19971224 (60)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Solola, Taofiq

LREP Keown & Associates

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN 0 Drawing Figure(s); 0 Drawing Page(s)

LN.CNT 848

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides novel β -lactamase inhibitors, which are structurally unrelated to the natural product and semi-synthetic β -lactamase inhibitors presently available, and which do not possess β -lactam pharmacophore. These new inhibitors are fully synthetic, allowing ready access to a wide variety of structurally related analogs. Certain embodiments of these new inhibitors also bind bacterial DD-peptidases, thus potentially acting both as β -lactamase inhibitors and as antibiotics.

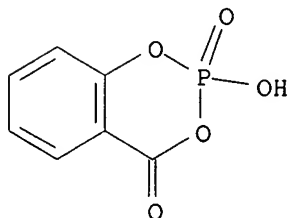
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 91746-64-4P 229344-36-9P 229344-44-9P

(phosphate and phosphonate β -lactamase and DD-peptidase inhibitors)

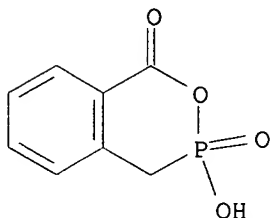
RN 91746-64-4 USPATFULL

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



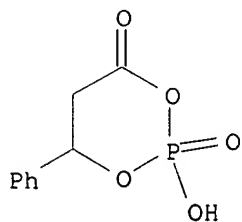
RN 229344-36-9 USPATFULL

CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)



RN 229344-44-9 USPATFULL

CN 1,3,2-Dioxaphosphorinan-4-one, 2-hydroxy-6-phenyl-, 2-oxide (9CI) (CA INDEX NAME)

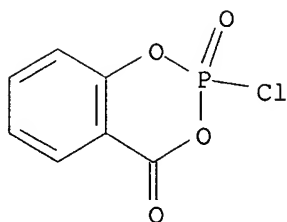


IT 5381-98-6P

(phosphate and phosphonate β -lactamase and DD-peptidase inhibitors)

RN 5381-98-6 USPATFULL

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-chloro-, 2-oxide (9CI) (CA INDEX NAME)



L51 ANSWER 3 OF 4 USPATFULL on STN

AN 2002:37887 USPATFULL

TI Acyl phosphonate inhibitors of beta-lactamases

IN Besterman, Jeffrey M., Baie D'Urfe, CANADA
 Rahil, Jubrail, Dollard Des Ormeaux, CANADA
 Pratt, Rex, Portland, CT, UNITED STATES

PI US 2002022607 A1 20020221

US 6599889 B2 20030729

AI US 2001-797308 A1 20010301 (9)

RLI Continuation-in-part of Ser. No. US 2000-582255, filed on 1 Sep 2000,
 PENDING A 371 of International Ser. No. WO 1998-US27518, filed on 23 Dec
 1998, UNKNOWN

PRAI US 1997-68837P 19971224 (60)

DT Utility

FS APPLICATION

LREP HALE AND DORR, LLP, 60 STATE STREET, BOSTON, MA, 02109

CLMN Number of Claims: 50

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1242

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides novel β -lactamase inhibitors, which are structurally unrelated to the natural product and semi-synthetic β -lactamase inhibitors presently available, and which do not possess a β -lactam pharmacophore. These new inhibitors are fully synthetic, allowing ready access to a wide variety of structurally related analogs. Certain embodiments of these new inhibitors also bind bacterial DD-peptidases, thus potentially acting both as β -lactamase inhibitors and as antibiotics.

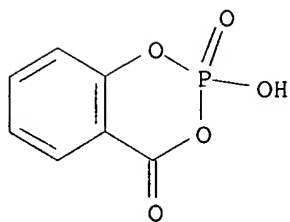
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **91746-64-4P 229344-36-9P 400605-09-6P**
400605-23-4P 400605-71-2P

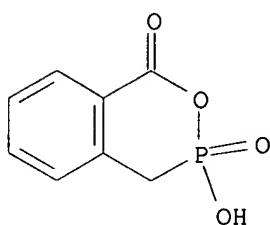
(preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of beta-lactamases and DD-peptidases)

RN 91746-64-4 USPATFULL

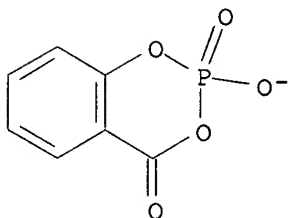
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



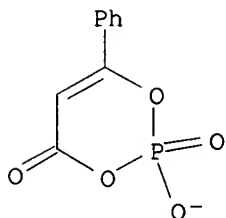
RN 229344-36-9 USPATFULL
 CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)



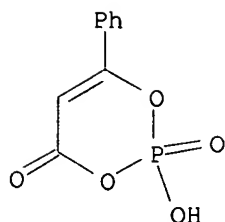
RN 400605-09-6 USPATFULL
 CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide, ion(1-) (9CI) (CA INDEX NAME)



RN 400605-23-4 USPATFULL
 CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide, ion(1-) (9CI) (CA INDEX NAME)



RN 400605-71-2 USPATFULL
 CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide (9CI) (CA INDEX NAME)



L51 ANSWER 4 OF 4 USPAT2 on STN
 AN 2002:37887 USPAT2
 TI Acyl phosphonate inhibitors of β -lactamases
 IN Besterman, Jeffrey M., Baie d'Urfe, CANADA
 Rahil, Jubrail, Dollard des Ormeaux, CANADA
 Pratt, Rex, Portland, CT, United States
 PA MethylGere, Inc., St. Laurent, CANADA (non-U.S. corporation)
 PI US 6599889 B2 20030729
 AI US 2001-797308 20010301 (9)
 RLI Continuation-in-part of Ser. No. US 582255
 PRAI US 1997-68837P 19971224 (60)
 DT Utility
 FS GRANTED
 EXNAM Primary Examiner: Solola, Taofiq
 LREP Keown & Associates
 CLMN Number of Claims: 18
 ECL Exemplary Claim: 1
 DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
 LN.CNT 1094

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides novel β -lactamase inhibitors, which are structurally unrelated to the natural product and semi-synthetic β -lactamase inhibitors presently available, and which do not possess a β -lactam pharmacophore. These new inhibitors are fully synthetic, allowing ready access to a wide variety of structurally related analogs. Certain embodiments of these new inhibitors also bind bacterial DD-peptidases, thus potentially acting both as β -lactamase inhibitors and as antibiotics.

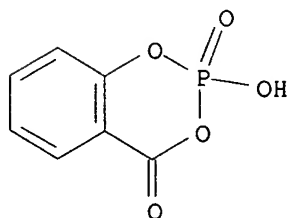
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 91746-64-4P 229344-36-9P 400605-09-6P
 400605-23-4P 400605-71-2P

(preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of beta-lactamases and DD-peptidases)

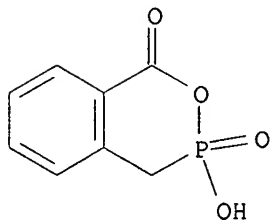
RN 91746-64-4 USPAT2

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



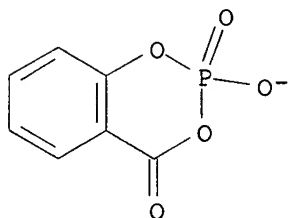
RN 229344-36-9 USPAT2

CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)



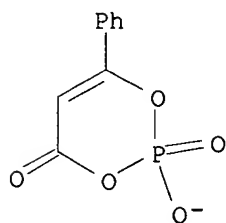
RN 400605-09-6 USPAT2

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide, ion(1-) (9CI) (CA INDEX NAME)



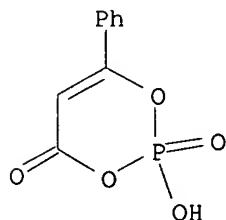
RN 400605-23-4 USPAT2

CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide, ion(1-) (9CI) (CA INDEX NAME)



RN 400605-71-2 USPAT2

CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide (9CI) (CA INDEX NAME)



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(FILE 'HOME' ENTERED AT 07:38:25 ON 08 DEC 2005)
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FILE 'HCAPLUS' ENTERED AT 07:38:45 ON 08 DEC 2005

L1 2 S (US20050119233 OR US20020022607 OR US6599889 OR US6608046)/PN
L2 2 S (US2003-628649# OR US2001-797308# OR US2000-582255# OR WO98-U
L3 2 S L1,L2
E BESTERMAN J/AU
L4 75 S E3-E8,E11
E RAHIL J/AU
L5 24 S E3-E6
E PRATT R/AU
L6 520 S E3-E28
E PRATT REX/AU
L7 11 S E3,E4
E METHYLGENE/PA,CS
L8 38 S E3-E10
E METHYL GENE/PA,CS
SEL RN L3

FILE 'REGISTRY' ENTERED AT 07:42:47 ON 08 DEC 2005

L9 67 S E1-E67
L10 1 S 9073-60-3
L11 60 S L9 AND P/ELS
L12 6 S L11 AND (OPOC3 OR OPOC3-C6)/ES
L13 STR
L14 10 S L13
L15 197 S L13 FUL
SAV TEMP L15 SHIAO628/A
L16 64 S L15 AND (OPOC3 OR OPOC3-C6)/ES
L17 64 S L12,L16
L18 133 S L15 NOT L17
L19 25 S L18 AND (C3H5O4P OR C8H4O8P2 OR C3H3O5P OR C10H9O4P OR C8H7O4
L20 24 S L19 NOT C6-C6/ES
L21 16 S L17 AND (C7H4BRO4P OR C9H6O5P OR C5H7O6P OR C9H9O5P OR C7H4O5
L22 14 S L21 NOT (13237-77-9 OR 13237-77-9/CRN)
L23 50 S L17 NOT L22
L24 38 S L20,L22,L12
SAV TEMP L24 SHIAO628A/A

FILE 'HCAOLD' ENTERED AT 08:09:22 ON 08 DEC 2005

L25 10 S L24
SEL AN
EDIT E68-E77 /AN /OREF

FILE 'HCAPLUS' ENTERED AT 08:09:57 ON 08 DEC 2005

L26 19 S E68-E77
SEL AN 2 4 5 7 9 11 13 19
L27 11 S L26 NOT E78-E93
L28 39 S L24
L29 6 S L3-L8 AND L27,L28
L30 10678 S L10
L31 13255 S BETA LACTAMASE
L32 3644 S PENICILLINASE
L33 6 S L27,L28 AND L30-L32

L34 6 S L29,L33
L35 29 S L28 AND (PY<=1997 OR PRY<=1997 OR AY<=1997)
L36 7 S L27 AND L35
L37 11 S L27,L36
L38 20 S L35 NOT L34,L37
L39 0 S L38 AND (PHARMACEUT? OR PHARMACOL?)/SC,SX
L40 1 S L38 AND (1 OR 63)/SC,SX
L41 7 S L24(L) (THU OR BAC OR PKT OR PAC OR DMA OR BIOL)/RL
L42 2 S L41 AND L35
L43 7 S L34,L40,L42
L44 2 S L24 AND BIOL+NT/RL AND L35
L45 7 S L43,L44
L46 7 S L45 AND L1-L8, L26-L45
L47 3 S L46 AND (PHARMACEUT? OR PHARMACOL?)/SC,SX
L48 6 S L46 AND L24(L) (THU OR BAC OR PKT OR PAC OR DMA OR BIOL)/RL
L49 7 S L46-L48

FILE 'REGISTRY' ENTERED AT 08:21:26 ON 08 DEC 2005

FILE 'HCAPLUS' ENTERED AT 08:21:36 ON 08 DEC 2005

FILE 'USPATFULL, USPAT2' ENTERED AT 08:21:54 ON 08 DEC 2005

L50 4 S L24
L51 4 S L50 AND A61K/IPC

FILE 'USPATFULL, USPAT2' ENTERED AT 08:22:23 ON 08 DEC 2005

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